

Genital Herpes Simplex Virus (HSV) Infection

GENITAL HERPES is a recurrent, incurable viral disease. Two serotypes of HSV have been identified: HSV-1 and HSV-2. Most cases of recurrent genital herpes are caused by HSV-2. On the basis of serologic studies, genital HSV-2 infection has been diagnosed in at least 45 million persons in the United States.

Most HSV-2-infected persons have not received a diagnosis of genital herpes. Such persons have mild or unrecognized infections that shed virus intermittently in the genital tract. Some cases of first-episode genital herpes are manifested by severe disease that might require hospitalization. Many cases of genital herpes are transmitted by persons who are unaware that they have the infection or are asymptomatic when transmission occurs.

Systemic antiviral drugs partially control the symptoms and signs of herpes episodes when used to treat first clinical episodes or recurrent episodes or when used as daily suppressive therapy. However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. Randomized trials indicate that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir. Valacyclovir is a valine ester of acyclovir with enhanced absorption after oral administration. Famciclovir, a prodrug of penciclovir, also has high oral bioavailability. Topical therapy with acyclovir is substantially less effective than the systemic drug, and its use is discouraged. The recommended acyclovir

dosing regimens for both initial and recurrent episodes reflect substantial clinical experience, expert opinion, and FDA-approved dosages.

First Clinical Episode of Genital Herpes

Management of patients with first clinical episode of genital herpes includes antiviral therapy and counseling regarding the natural history of genital herpes, sexual and perinatal transmission, and methods to reduce such transmission. Five percent to 30% of first-episode cases of genital herpes are caused by HSV-1, but clinical recurrences are much less frequent for HSV-1 than HSV-2 genital infection. Therefore, identification of the type of the infecting strain has prognostic importance and may be useful for counseling purposes.

Recommended Regimens

Acyclovir 400 mg orally three times a day for 7-10 days,

OR

Acyclovir 200 mg orally five times a day for 7-10 days,

OR

Famciclovir 250 mg orally three times a day for 7-10 days,

OR

Valacyclovir 1 g orally twice a day for 7-10 days.

NOTE: Treatment may be extended if healing is incomplete after 10 days of therapy.

Higher dosages of acyclovir (i.e., 400 mg orally five times a day) were used in treatment studies of first-episode herpes proctitis and first-episode oral infection, including stomatitis or pharyngitis. It is unclear whether these forms of mucosal infection require higher doses of acyclovir than used for genital herpes. Valacyclovir and famciclovir

probably are also effective for acute HSV proctitis or oral infection, but clinical experience is lacking.

Counseling is an important aspect of managing patients who have genital herpes. Although initial counseling can be provided at the first visit, many patients benefit from learning about the chronic aspects of the disease after the acute illness subsides. Counseling of these patients should include the following:

- Patients who have genital herpes should be told about the natural history of the disease, with emphasis on the potential for recurrent episodes, asymptomatic viral shedding, and sexual transmission.

- Patients should be advised to abstain from sexual activity when lesions or prodromal symptoms are present and encouraged to inform their sex partners that they have genital herpes. The use of condoms during all sexual exposures with new or uninfected sex partners should be encouraged.

- Sexual transmission of HSV can occur during asymptomatic periods. Asymptomatic viral shedding occurs more frequently in patients who have genital HSV-2 than HSV-1 infection and in patients who have had genital herpes for <12 months. Such patients should be counseled to prevent spread of the infection.

- The risk for neonatal infection should be explained to all patients, including men. Childbearing-age women who have genital herpes should be advised to inform health-care providers who care for them during pregnancy about the HSV infection.

- Patients having a first episode of genital herpes should be ad-

vised that a) episodic antiviral therapy during recurrent episodes might shorten the duration of lesions and b) suppressive antiviral therapy can ameliorate or prevent recurrent outbreaks.

Recurrent Episodes of HSV Disease

Most patients with first-episode genital HSV-2 infection will have recurrent episodes of genital lesions. Episodic or suppressive antiviral therapy might shorten the duration of lesions or ameliorate recurrences. Because many patients benefit from antiviral therapy, options for treatment should be discussed with all patients.

When treatment is started during the prodrome or within 1 day after onset of lesions, many patients who have recurrent disease benefit from episodic therapy. If episodic treatment of recurrences is chosen, the patient should be provided with antiviral therapy, or a prescription for the medication, so that treatment can be initiated at the first sign of prodrome or genital lesions.

Daily suppressive therapy reduced the frequency of genital herpes recurrences by $\geq 75\%$ among patients who have frequent recurrences (i.e., six or more recurrences per year). Safety and efficacy have been documented among patients receiving daily therapy with acyclovir for as long as 6 years, and with valacyclovir and famciclovir for 1 year. Suppressive therapy has not been associated with emergence of clinically significant acyclovir resistance among immunocompetent patients. After 1 year of continuous suppressive therapy, discontinuation of therapy should be discussed with the patient to assess the patient's psychological adjustment of genital herpes and rate of recurrent episodes, as the frequency of recurrences decreases over time in many patients. Insufficient experience with famciclovir and valacyclovir prevents recommendation of these drugs for >1 year.

Suppressive treatment with acyclovir reduces but does not eliminate asymptomatic viral shedding. Therefore, the extent to which suppressive therapy may prevent HSV transmission is unknown.

Recommended Regimens for Episodic Recurrent Infection

Acyclovir 400 mg orally three times a day for 5 days,
OR
Acyclovir 200 mg orally five times a day for 5 days,
OR
Acyclovir 800 mg orally twice a day for 5 days,
OR
Famciclovir 125 mg orally twice a day for 5 days,
OR
Valacyclovir 500 mg orally twice a day for 5 days.

Recommended Regimens for Daily Suppressive Therapy

Acyclovir 400 mg orally twice a day,
OR
Famciclovir 250 mg orally twice a day,
OR
Valacyclovir 250 mg orally twice a day,
OR
Valacyclovir 500 mg orally once a day,
OR
Valacyclovir 1,000 mg orally once a day.

Valacyclovir 500 mg once a day appears less effective than other valacyclovir dosing regimens in patients who have very frequent recurrences (i.e., ≥ 10 episodes per year). Few comparative studies of valacyclovir and famciclovir with acyclovir have been conducted. The results of these studies suggest that valacyclovir and famciclovir are comparable to acyclovir in clinical outcome. However, valacyclovir and famciclovir may provide increased ease in administration, which is an important consideration for prolonged treatment.

Severe Disease

IV therapy should be provided for patients who have severe disease or complications necessitating hospitalization, such as disseminated infection, pneumonitis, hepatitis, or complications of the central nervous system (e.g., meningitis or encephalitis).

Recommended Regimen

Acyclovir 5-10 mg/kg body weight IV every 8 hours for 5-7 days or until clinical resolution is attained.

Management of Sex Partners

The sex partners of patients who have genital herpes are likely to benefit from evaluation and coun-

seling. Symptomatic sex partners should be evaluated and treated in the same manner as patients who have genital lesions. However, most persons who have genital HSV infection do not have a history of typical genital lesions. These persons and their future sex partners may benefit from evaluation and counseling. Thus, even asymptomatic sex partners of patients who have newly diagnosed genital herpes should be questioned concerning histories of typical and atypical genital lesions, and they should be encouraged to examine themselves for lesions in the future and seek medical attention promptly if lesions appear.

Most of the available HSV antibody tests do not accurately discriminate between HSV-1 and HSV-2 antibodies, and their use is not currently recommended. Sensitive and type-specific serum antibody assays may become commercially available and contribute to future investigation strategies.

Special Considerations

Allergy, Intolerance, or Adverse Reactions

Allergic and other adverse reactions to acyclovir, valacyclovir, and famciclovir are infrequent. Desensitization to acyclovir has been described previously.

HIV Infection

Immunocompromised patients might have prolonged and/or severe episodes of genital or perianal herpes. Lesions caused by HSV are relatively common among HIV-infected patients and may be severe, painful, and atypical. Intermittent or suppressive therapy with oral antiviral agents is often beneficial.

The dosage of antiviral drugs for HIV-infected patients is controversial, but clinical experience strongly suggests that immunocompromised patients benefit from increased doses of antiviral drugs. Regimens such as acyclovir 400 mg orally three to five times a day, as used for other immunocompromised patients, have been useful. Therapy should be continued until clinical resolution is attained. Famciclovir 500 mg twice a day has been effective in decreasing both the rate of recurrences and the rate of sub-

clinical shedding among HIV-infected patients. In immunocompromised patients, valacyclovir in doses of 8 g per day has been associated with a syndrome resembling either hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. However, in the doses recommended for treatment of genital herpes, valacyclovir, acyclovir, and famciclovir probably are safe for use in immunocompromised patients. For severe cases, acyclovir 5 mg/kg IV every 8 hours may be required.

If lesions persist in a patient receiving acyclovir treatment, resistance of the HSV strain to acyclovir should be suspected. Such patients should be managed in consultation with an expert. For severe cases caused by proved or suspected acyclovir-resistant strains, alternate therapy should be administered. All acyclovir-resistant strains are resistant to valacyclovir, and most are resistant to famciclovir. Foscarnet, 40 mg/kg body weight IV every 8 hours until clinical resolution is attained, is often effective for treatment of acyclovir-resistant genital herpes. Topical cidofovir gel 1% applied to the lesions once daily for 5 consecutive days also might be effective.

Pregnancy

The safety of systemic acyclovir and valacyclovir therapy in pregnant women has not been established. Glaxo-Wellcome, Inc., in cooperation with CDC, maintains a registry to assess the use and effects of acyclovir and valacyclovir during pregnancy. Women who receive acyclovir or valacyclovir during pregnancy should be reported to this registry; telephone (800) 722-9292, extension 38465.

Current registry findings do not indicate an increased risk for major birth defects after acyclovir treat-

ment (i.e., in comparison with the general population). These findings provide some assurance in counseling women who have had prenatal exposure to acyclovir. The accumulated case histories represent an insufficient sample for reaching reliable and definitive conclusions regarding the risks associated with acyclovir treatment during pregnancy. Prenatal exposure to valacyclovir and famciclovir is too limited to provide useful information on pregnancy outcomes.

The first clinical episode of genital herpes during pregnancy may be treated with oral acyclovir. In the presence of life-threatening maternal HSV infection (e.g., disseminated infection, encephalitis, pneumonitis, or hepatitis), acyclovir administration IV is indicated. Investigations of acyclovir use among pregnant women suggest that acyclovir treatment near term might reduce the rate of abdominal deliveries among women who have frequently recurring or newly acquired genital herpes by decreasing the incidence of active lesions. However, routine administration of acyclovir to pregnant women who have a history of recurrent genital herpes is not recommended at this time.

Perinatal Infection

Most mothers of infants who acquire neonatal herpes lack histories of clinically evident genital herpes. The risk for transmission to the neonate from an infected mother is high among women who acquire genital herpes near the time of delivery (30%-50%) and is low among women who have a history of recurrent herpes at term and women who acquire genital HSV during the first half of pregnancy (3%). Therefore, prevention of neonatal herpes should emphasize prevention of acquisi-

tion of genital HSV infection during late pregnancy. Susceptible women whose partners have oral or genital HSV infection, or those whose partners' infection status is unknown, should be counseled to avoid unprotected genital and oral sexual contact during late pregnancy. The results of viral cultures during pregnancy do not predict viral shedding at the time of delivery, and such cultures are not indicated routinely.

At the onset of labor, all women should be examined and carefully questioned regarding whether they have symptoms of genital herpes. Infants of women who do not have symptoms or signs of genital herpes infection or its prodrome may be delivered vaginally. Abdominal delivery does not completely eliminate the risk for HSV infection in the neonate.

Infants exposed to HSV during birth, as proven by virus isolation or presumed by observation of lesions, should be followed carefully. Some authorities recommend that such infants undergo surveillance cultures of mucosal surfaces to detect HSV infection before development of clinical signs. Available data do not support the routine use of acyclovir for asymptomatic infants exposed during birth through an infected birth canal, because the risk for infection in most infants is low. However, infants born to women who acquired genital herpes near term are at high risk for neonatal herpes, and some experts recommend acyclovir therapy for these infants. Such pregnancies and newborns should be managed in consultation with an expert. All infants who have evidence of neonatal herpes should be promptly evaluated and treated with systemic acyclovir. Acyclovir 30-60 mg/kg/day for 10-21 days is the regimen of choice.